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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/669,187	KRIEG ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-9,15-39,52-54,77,85,88-94,98 and 107-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-9,15-39,52-54,77,85,88-94,98 and 107-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/12/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 2, 10-14, 40-51, 55-76, 78-84, 86-87, 95-97 and 99-106 have been cancelled.

Claims 1, 3, 16-18, 22-33, 52-54, 77, 85, 88-94 and 98 have been amended.

Claims 107-112 have been added.

2. Claims 1, 3-9, 15-39, 52-54, 77, 85, 88-94, 98 and 107-112 are pending and under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains New Grounds of Rejections.

Information Disclosure Statement

5. The information disclosure statement filed 2/7/2005 fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information

disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered. If applicant wishes to have the document submitted on 2/7/2005 considered, applicant should cite the relevant document on a PTO-1449 for consideration.

Objections/Rejections Withdrawn

6. The objections of claims 1, 59, 76-77, 86 and 88-89 as being drawn to non-elected inventions and for being in improper dependent form are withdrawn in view of amendments to the claims.

7. The rejections of claims 11-15, 61, 85 and 98, parts a-d, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention are withdrawn in view of the amendments to the claims.

8. The rejection of claims 1-16, 18-24, 26-39, 45-61, 74-77, 85-94 and 98 under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with the claims is withdrawn in view of the amendments to the claims and in view of the New Grounds of Rejection below for lack of enablement.

9. The rejection of claims 1-13, 16-19, 21-22, 24-25, 37, 39, 77, 85-87, 90-92, 94 and 98 under 35 U.S.C. 102(a) as anticipated by Jones et al is withdrawn in view of the amendments to the claims.

10. The rejection of claims 1-13, 16-19, 21, 24-25, 30, 33-34, 36-39, 77, 85-87, 94 and 98 under 35 U.S.C. 102(e) as anticipated by Krieg et al is withdrawn in view of the amendments to the claims.

11. The rejection of claims 1-13, 16-21, 23-25, 30-31, 33-34, 36-39, 77, 85-87, 92, 94 and 98 under 35 U.S.C. 102(b) as anticipated by Davis et al is withdrawn in view of the amendments to the claims.

12. The rejection of claims 1-5, 10-13, 16, 18-21, 25, 30-33, 36-39, 45-49, 52-61, 77, 85-87, 90, 94 and 98 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 46-58, 64-66, 71-74, 77-78, 80-81, 84, 89-90, 95-96 and 98 of copending USSNs 10/613,228; 10/613,739; 10/613,736 in view of Krieg et al (U.S. Patent 6,239,116 B1, 10/30/1997, Ids reference A38) is withdrawn in view of the amendments to the claims.

13. The rejection of claims 1-13, 16-20, 24-25, 30, 34-35, 37-39, 54, 56, 77, 85-87, 94 and 98 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5, 7-9, 16-18, 20-21, 23-25, 27-30, 34 and 40-41 of copending Application No. 10/272,502 in view of Krieg et al (U.S. Patent 6,239,116 B1, 10/30/1997, Ids reference A38) is withdrawn in view of the amendments to the claims.

Response to Arguments

14. The objection to the specification for containing USSNs of U.S. Patent applications that have now issued as U.S. Patents is maintained.

The response filed 12/27/2004 and the amendment submitted therewith updated most of the disclosed USSNs with their corresponding U.S. patent numbers, however, USSN 09/191,170 is now U.S. Patent 6,429,199. Applicant is required to update the status of USSN 09/191,170 to indicate "now U.S. Patent No. 6,429,199. Furthermore, applicant's amendment to the specification at page 24 includes an incorrect U.S. Patent number for USSN 08/960,774. The correct U.S. Patent No. for USSN 08/960,774 is 6,239,116.

Appropriate correction is required.

New Grounds of Objections/Rejections

15. Claims 23 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite for reciting "free of unmethylated CpG dinucleotides" in claim 23. Does the phrase mean that the T-rich immunostimulatory nucleic acid comprises methylated CpG dinucleotides or is it free of CpG dinucleotides or is some other meaning contemplated by the phrase? Similarly, for claim 24, does the phrase "free of methylated CpG dinucleotides" mean that the T-rich immunostimulatory nucleic

acid comprises unmethylated CpG dinucleotides or is it free of CpG dinucleotides or is some other meaning contemplated by the phrase? One of skill in the art would not be reasonable apprised of the chemical structure of the claimed T-rich immunostimulatory nucleic acid and hence, would not be reasonably apprised of the metes and bounds of the invention.

16. Claims 1, 3, 5, 15-39, 52-54, 77, 85, 88-94, 98 and 107-112 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (see MPEP 2164).

In the instant case, the claims encompass methods of stimulating an immune response in a subject comprising administering a T-rich immunostimulatory nucleic acid

that is 8-100 nucleotides in length and has a nucleotide composition greater than 60% T or is 8-100 nucleotides in length and lacks a CpG motif. Therefore, the claims encompass a genus of possibly thousands of different nucleic acids considering every possible T-rich immunostimulatory oligonucleotide that is 8-100 nucleotides in length having a nucleotide composition greater than 60% T. The specification indicates one sub-genus of CpG containing oligonucleotides, which comprise a T-rich motif represented by the formula 5'-$X_1X_2TTTTX_3X_4$-3', and disclosed as capable of inducing an immune response, thus, indicating distinct structural and functional properties of one sub-genus of molecules embraced by the claims. However, as mentioned above, the claims encompass any T-rich immunostimulatory nucleic acid that is 8-100 nucleotides in length and having greater than 60% T. Therefore, the claims encompass a number of sub-genuses of T-rich immunostimulatory nucleic acids such as antisense oligonucleotides and methylated or unmethylated CpG containing oligonucleotides, T-rich nucleic acids lacking a backbone modification as well as others.

Per the *Enzo* court's example, (*Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (CA FC 2002) at 1616) of a description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) couched "in terms of its function of lessening inflammation of tissues" which, the court stated, "fails to distinguish any steroid from others having the same activity or function" and the expression "an antibiotic penicillin" fails to distinguish a particular penicillin molecule from others possessing the same activity and which therefore, fails to satisfy the written description requirement. Similarly, a T-rich immunostimulatory nucleic acid that is 8-100 nucleotides in length

that stimulates an immune response does not distinguish T-rich immunostimulatory nucleic acids from others having the same activity or function and as such, does not satisfy the written-description requirement. Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed genus. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

17. Claims 1, 3-9, 15-37, 39, 52-54, 77, 85, 88-94, 98 and 107-112 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of stimulating an immune response comprising administering phosphorothioate T-rich immunostimulatory nucleic acid having 100% T nucleotide content that is 8-100 nucleotides in length, does not reasonably provide enablement for all of the embodiments encompassed by the claims. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention:

The claims are drawn to methods of stimulating an immune response in a subject, including innate and systemic immune responses comprising administering a T-rich immunostimulatory nucleic acid that is 8-100 nucleotides in length and has a nucleotide composition that is greater than 60% T and optionally comprises a CpG motif or is 8-100 nucleotides in length and lacks a CpG (claims 107-109 and 112) and the method further comprises administering an antibody or an antigen.

The breadth of the claims:

The breadth of the claims is very broad. For instance the claims encompass stimulating any immune response in a subject comprising administering a T-rich immunostimulatory nucleic acid that is 8-100 nucleotides in length and has a nucleotide composition that is greater than 60% T and the T-rich nucleic acid may optionally comprise a CpG motif. Thus, the claims are drawn to a genus of thousands of possible

T-rich nucleic acids of various lengths and chemical composition that do not require a backbone modification (e.g., phosphorothioate modification; claim 1) and may optionally comprise methylated or unmethylated CpG dinucleotides. Further, the claims encompass the co-administration or the subsequent administration of just any antibody that binds some arbitrary cell surface antigen or co-administration or the subsequent administration of just any peptide antigen. Thus, the claims encompass stimulating an immune response in any subject, including humans for therapy of any pathological disease, including diseases not yet identified.

The unpredictability of the art and the state of the prior art:

The state of the prior art for T-rich immunostimulatory nucleic acids at the time of filing the instant application was a nascent technology. As noted in *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art.

Regarding the use immunostimulatory nucleic acids, the art recognizes a number of specific characteristics of the oligonucleotide, which are critical for its function as an immunostimulatory molecule. For instance, for the claimed T-rich nucleic acids that comprise a CpG dinucleotide, Agrawal et al. (Trends in Mol. Med., 2002; 8:114-121) teaches, "The presence of unmethylated CpG dinucleotide is essential for the induction of immunostimulatory activity..." (See p. 1 14, bottom of second column).

Hartmann et al. (J. Immunology, 2000; 164:1617-1624) teaches that the oligonucleotide must be protected from nuclease degradation in order to be effective in

vivo. Specifically, Hartmann teaches, "To have in vivo clinical utility, ODN must be administered in a form that protects them against nuclease degradation. The native phosphodiester internucleotide linkage can be modified to become highly nuclease resistant via replacement of one of the non-bridging oxygen atoms with a sulfur, which constitutes phosphorothioate ODN." (see p. 1618, first column).

Vollmer et al (Antisense and Nucleic Acid Drug Development, 12:165-175, 2002, cited previously) teach specific sequence requirements of CpG-free phosporothioate oligodeoxynucleotides (ODNs) for *in vitro* immunostimulatory activity, specifically the thymidine content and the length of phosporothioate-ODNs determine the immunostimulatory potential and the importance of ODNs having a phosphorothioate backbone modification (see entire document). Vollmer et al teach that a short polythymidine ODN with 18 nucleotides showed background activity, whereas increasing the length resulted in a progressively strong increase in stimulation for polythymidine ODNs 2195 (21 bases), 2183 (24 bases), and 2194 (27 bases) (see page 169, left column and Figure 2). According to Vollmer et al, short non-CpG phosphorothioate ODN induces only minimal stimulation *in vivo* as well as *in vitro* and that ODNs equal or greater than 24 nucleotides are needed to induce stronger stimulation (see page 173, right column) and Vollmer et al states "Nevertheless, *in vitro* longer non-CpG T-rich ODNs are always less efficient and potent than CpG ODNs, and, therefore, they might induce weaker *in vivo* effects that are not sufficient to mediate efficiently a Th1-dominated immune response." Vollmer et al teaches that the mechanism of immune activation by non-CpG ODNs remains to be elucidated. In

agreement with the teachings of Vollmer, McCluskie et al (Vaccine, 19:2657-2660, 2001, cited previously) teaches a polythymidine nucleic acid twenty nucleotides in length (ODN 1983), which did not have an immunostimulatory effect in immunized mice (see page 2658 and Figures 1-2). Further, Jones et al (Vaccine, 17:3065-3071, 19999, cited previously) teach a T-rich immunostimulatory nucleic acid lacking CpG dinucleotides as a negative control for testing ODNs *in vivo* for their adjuvant activities in monkeys (see page 3066, right column and page 3067 and Figures 1-2).

Weiner G. J. (Journal of Leukocyte Biology, 68:455-463, 2000) cautions that the clinical effects of CpG ODNs have not yet been explored, more needs to be learned about the heterogeneous responses that occur based on host organism, cell subset, or CpG ODN sequence and "further work with CpG ODN in both the laboratory and the clinic is needed before we can know their true promise as investigational immunological and therapeutic agents." (see page 461). Thus, given the limited knowledge in the art about the immunostimulatory properties of T-rich immunostimulatory nucleic acids and the fact that this technology was evolving at the time of filing, the cautions of Weiner are even more applicable to the presently claimed T-rich immunostimulatory nucleic acids. Further, in view of the teachings of Vollmer et al, indicating that T-rich nucleic acids are minimally immunostimulatory and sub-optimal relative to CpG immunostimulatory nucleic acids, one of skill in the art could not predictably extrapolate the teachings in the CpG art to T-rich immunostimulatory nucleic acids with a reasonable expectation of success.

Working Examples and Guidance in the Specification

The specification does not have a single working example demonstrating the *in vivo* administration of a T-rich immunostimulatory nucleic acid that is greater than 60% T and is 8-100 nucleotides in length as presently claimed. The specification at page 4 discloses 115 T-rich nucleic aids (see SEQ ID numbers at page 4, line 25 to page 5, line 2), however, only 21 of these T-rich nucleic acid sequences contain greater than 60% T (i.e., SEQ ID numbers 60-61, 226, 272-273, 305, 430-433, 499, 556, 692-694, 794 867, 868 and 911-913) and of these T-rich nucleic acids the longest is 29 nucleotides long (i.e., SEQ ID NO:305). None of these disclosed T-rich nucleic acids are greater than 29 nucleotides in length and none of these disclosed T-rich immunostimulatory nucleic acids have been assayed for their *in vivo* immunostimulatory properties. "[A] specification which describes' does not necessarily also enable' one skilled in the art to make or use the claimed invention." See *In re Armbruster*, 512 F.2d 676, 677, 185 USPQ 152, 153 (CCPA 1975). Example 2 at page 126 of the specification teaches that the pure poly-T sequence of SEQ ID NO:433 stimulates NK activity *in vitro* and acknowledges that "the T content of an ODN is an important determination of its immune stimulatory effect." (see page 127, lines 19-20). With respect to B cell activation, the specification at page 134 discloses that pure poly-T sequences, SEQ ID NO:913 (Poly T, 18 bases), SEQ ID NO:911 (Poly T, 27 bases) and SEQ ID NO:1094 (Poly T, 30 bases) stimulate B cells (see Figure 5) and shows that the length of the sequence for poly T ODNs has an important impact on its activity. Further, example 7 and Figure 7 shows that SEQ ID Nos:433 (ODN 2183) and 911 (ODN 2194) stimulate

NK cells as well as induce monocyte stimulation, but have different levels of activity (see page 137). There are no examples or guidance in applicant's specification to assist one skilled in the art in the administration of a T-rich immunostimulatory nucleic acid and an antibody, or an antigen or both an antibody and an antigen as encompassed by the claims. There is no guidance in applicant's specification with respect to optimal routes of administration or effective dosages for stimulating a specific type of immune response by administering a T-rich nucleic acid that is greater than 60% T and is 8-100 nucleotides in length. According to Vollmer et al, the route of administration can have an effect on the immunomodulatory effects, since substantial immunostimulatory effects were observed after oral, but not parental delivery (see page 173, right column). The specification as well as the prior art does not teach that T-rich nucleic acids as defined by the claims effectively enhance FcR-mediated antibody dependent cellular cytotoxicity (ADCC) or stimulate a systemic immune response when administered to a subject.

Quantity of Experimentation

Considering the breadth of the claims and the limited working examples and lack of guidance in the specification, one of skill in the art would be required to perform additional experimentation in order to be able to effectively use the invention to the full scope of the claims with a reasonable expectation of success. Additional experimentation would be required in order to use any T-rich immunostimulatory nucleic acid that is 8-100 nucleotides in length and having a nucleotide composition greater than 60% T given the unpredictability in the art. In applications directed to inventions in

arts where the results are unpredictable, the disclosure of a single species usually does not provide adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 193). In the instant case, applicant is relying on the *in vitro* stimulation of B cells, NK cells and monocytes using a single T-rich species greater than 60% T, i.e., pure poly T of various lengths to support the broad genus of T-rich nucleic acids having greater than 60% T for stimulating any type of immune response in a subject, which is merely an invitation to one skilled in the art to experiment and discover for themselves how to practice the claimed invention. For instance, one of skill in the art would have to synthesize and screen millions of T-rich immunostimulatory nucleic acids that are 8-100 nucleotides in length, have a nucleotide content of greater than 60% T and have the various backbone modifications or lack a backbone modification as embraced by the claims for immune stimulatory properties, then test for *in vivo* immune stimulation to determine if a correlation exists between the *in vitro* and *in vivo* properties for each of the T-rich nucleic acids and in view of the teachings in the specification as well as in the prior art, indicating that the length and content of the T-rich nucleic acids are important determinants of its immune stimulatory effect, one of skill in the art would have to optimize each T-rich nucleic acid individually. Additionally, one of skill in the art would have to optimize routes for administration, dosages and determine which antigen or antibody administered subsequently or co-administered with the T-rich immunostimulatory nucleic acid would be therapeutically effective in subjects. Also, additional experimentation would have to be done in order to overcome the teaching in the art that the ODNs must be administered in a form that protects them from nuclease

degradation in order to be effective. The amount of additional experimentation is deemed to be undue because in order to practice the full scope of the claimed invention with a reasonable expectation of success, one of skill in the art would have to show evidence overcoming art recognized problems that the broadly claimed T-rich nucleic acids effectively induce an immune response in a subject. By its own terms the instant application describes methods for "screening" and "evaluating" the effect of various T-rich immunostimulatory nucleic acids having greater than 60% T on the various immune responses of a subject. "Nascent technology, however, must be enabled with a specific and useful teaching." *Chiron Corp. v. Genetech Inc.,* 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004).

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

There is insufficient evidence or nexus that would lead the skilled artisan to predict the ability to induce an immune response in a non-rodent subject comprising administering a T-rich (with or without a CpG dinucleotide) nucleic acid that is 8-100 nucleotides in length and has a nucleotide content greater than 60% T. The specification provides insufficient guidance or direction to assist the skilled artisan in extrapolating data obtained by *in vitro* stimulation of a few selected subsets of immune cells, i.e., B cells, Nk cells and monocytes with a single species of a T-rich nucleic acid (pure poly T of various lengths) to stimulating any immune response in a subject by administering any T-rich nucleic acid that is 8-100 nucleotides in length and is greater

than 60% T as defined by the claims, particularly in view of the teachings of Agrawal et al, Hartmann et al, Vollmer et al, McCluskie et al, Jones et al and Weiner G.J.

In view of the lack of the predictability of the art to which the invention pertains the lack of established clinical protocols for effective therapies for T-rich immunostimulatory nucleic acids that are greater than 60 % T, undue experimentation would be required to practice the claimed T-rich immunostimulatory nucleic acids with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed T-rich immunostimulatory nucleic acids and absent working examples providing evidence which is reasonably predictive that the claimed T-rich immunostimulatory nucleic acids having greater than 60% T are effective for inducing an immune response in a subject, commensurate in scope with the claimed invention.

Response to Arguments

As applicable to the above new grounds of rejection under 35 U.S.C. 112, first paragraph, enablement, the response filed 12/27/2004 has been carefully considered, but is deemed not to be persuasive.

Applicant argues that Figure 5 demonstrates that T-rich nucleic acids of 18 nucleotides stimulate B cells and example 12, which showed that immunostimulatory nucleic acids without CpG motifs were negative or weak were performed at a single dose and at that dose non-CpG nucleic acids were characterized as negative or weak and applicant points to figure 5, which shows that pure poly T nucleic acids of various lengths are immunostimulatory at higher doses. Applicant argues that the results of

Vollmer et al are dosage specific and that for every T-rich nucleic acid there is an optimal dose which, may not be reflected in the data of Vollmer et al and applicant argues that the dose of the T-rich nucleic acid of McCluskie may not be optimal and the teachings of Jones et al only used a single dose of nucleic acid and that dose was clearly optimized for CpG nucleic acid effect. In response to applicant's arguments, applicant's arguments are evidence that considerable additional experimentation would have to be conducted since each of the millions of different T-rich nucleic acids encompassed by the broad claims would have to be optimized individually since as evidenced by the instant specification and in the teachings of the prior art that the T content and the length of the T-rich immunostimulatory nucleic acid are important determinants of its immune stimulatory effect.

Applicant argues that the specification teaches the parameters of the nucleic acids to be used in the claimed methods, such as the T-rich nucleic acids are capable of immune stimulation independent of their CpG content and the specification teaches administration of these nucleic acids to subjects including formulations, routes of administration and effective amounts and points to various pages of the specification. Applicant cites MPEP 2164.01(c) stating "if a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied." Applicant concludes the amount of direction and guidance provided in the specification is sufficient. In response to these arguments and as set forth in the new grounds of rejection above, the teachings in the specification are limited with respect to the broad

scope of the claims. A review of the pages of the specification pointed to by applicant only provide some general guidelines with respect to the T-rich nucleic acids as well as formulations, administration routes and effective amounts. These descriptions, without more precise guidelines, amount to little more than "a starting point, a direction for further research." *Genentech*, 108 F.3d at 1366. *See also Calgene*, 188 F.3d at 1374 ("the teachings set forth in the specification provide no more than a 'plan' or 'invitation' for those of skill in the art to experiment practicing [the claimed invention]; they do not provide sufficient guidance or specificity as to how to execute that plan"); *National Recovery Technologies*, 166 F.3d at 1198 (stating that patent-in-suit "recognizes a specific need... and suggests a theoretical answer to that need. It provides a starting point from which one of skill in the art can perform further research in order to practice the claimed invention, but this is not adequate to constitute enablement"). The instant specification does not describe the claimed invention in terms that will "enable any person skilled in the art... to make and use" the invention commensurate in scope with the claims without undue experimentation. At most, the specification will enable a person of ordinary skill in the art to attempt to discover how to practice the claimed invention. In response to applicant's arguments that the in vitro data presented in the specification is correlative to the claimed in vivo methods is insufficient as it is considered only an opinion, without data supporting the opinion.

Therefore, these arguments are not persuasive as applied to the above new grounds of rejections for lack of enablement.

18. Claim 38 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim broadly encompasses gene therapy, wherein the claimed method of inducing an immune response in a subject comprising administering a T-rich immunostimulatory nucleic acid and further comprises administration of a nucleic acid vector encoding an antigen.

The specification teaches in vitro stimulation of B cell, NK cells and monocytes comprising administering a pure poly T nucleic acid of various lengths (18, 27 and 30 nucleotides in length). The specification does not teach administration of a T-rich nucleic acid having greater that 60% T and a separate nucleic acid vector encoding an antigen that induces an immune response. There are no working examples in applicant's specification to guide the skilled artisan in practicing a method of administration of a T-rich nucleic acid having greater that 60% T and a separate nucleic acid vector encoding an antigen that induces an immune response.

The state of the art for gene therapy as discussed by Vile et al (Gene Therapy, Vol. 7, pp. 2-8, 2000) is unpredictable. Vile teaches:

> The problems which gene therapy for cancer will take into the next millennium focus far less on the choice of therapeutic gene(s) to be used than on the means of delivering them. There is already a battery of genes that we know are very effective in killing cells, if they can be expressed at the right site and at appropriate levels. Nonetheless, until the perfect vector is developed, the choice of gene will remain crucially important in order to compensate for the deficiencies of the vectors we currently have available (page 2, 1st paragraph, left column). Whatever its mechanism, no single genes can be a serious contender unless it

has a demonstrable bystander effect (page 2, right column). The requirement for such a bystander effect stems directly from the poor delivery efficiency provided by current vectors (page 2, right column).

A genuine ability to target delivery systems to tumor cells distributed widely throughout the body of a patient would simultaneously increase real titers and efficacy. In truth, no such systemically targeted vectors exist yet. Injection of vectors into the bloodstream for the treatment of cancer requires not only that the vectors be targeted (to infect only tumor cells) but also that they by protected (from degradation, sequestration or immune attack) for long periods of time so that they can reach the appropriate sites for infection. Moreover, having reached such sites, the vectors must be able to penetrate into the tumor from the bloodstream before carrying out their targeted infection (page 4, bottom left column and top right column).

In addition, Rochlitz C. F. (Swiss Medicine Weekly, 131:4-9, 2001) teaches:

"that none of the more than one hundred clinical studies performed so far had formally proven efficacy of the approach [gene therapy] in any human disease. Although anecdotal reports of tumor responses are becoming more frequent in several human malignancies, the situation has not changed dramatically." (See page 8, bottom of page). Rochlitz continue "Main problems are still the lack of vectors with high transduction efficiency in vivo, the low tumor specificity of available systems, and our incomplete knowledge of molecular tumor pathology." (see pages 8-9).

Thus, at the time the application was filed, the state of the art for gene therapy was considered highly unpredictable.

Furthermore, it would take one skilled in the art an undue amount of experimentation to determine what route of administration (*e.g.* intravenous, dermal, nasal, rectal, vaginal, inhalation, or topical administration) would result in a therapeutic response using a recombinant virus, lentivirus, adenovirus and retrovirus comprising the nucleic acid encoding the antigen. The state of the art for the route of administration for gene therapy as exemplified by Verma et al, Nature, Vol. 389, No. 6648, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders,

the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

Therefore, the skilled artisan at the time the invention was made recognized the lack of predictability of the nature of the art and state of the prior art to which the instant invention pertains. Also, such disclosures clearly indicate that the amount of direction or guidance presented in the specification is limited, and would not permit a person skilled in the art to use the invention without undue experimentation at the time the invention was made.

In view of the lack of predictability of the art to which the invention pertains, the lack of established clinical protocols for effective gene therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for decreasing the volume of solid tumors in a patient, commensurate in scope with the claimed invention.

19. Claims 1, 3-7, 15-16, 18-19, 21-25, 77, 85, 88-92, 94 and 112 are rejected under 102(b) as anticipated by Liang et al (Journal of Clinical Investigation, 98(5):1119-1129, September 1996, Ids reference C99 filed 7/12/2004).

The claims are drawn to a method of stimulating an immune response in a subject comprising administering a T-rich immunostimulatory nucleic acid that is 8-100 nucleotides in length and has a nucleotide composition greater than 60% T, wherein the poly T comprises 5' TTTT 3', or 5'-X_1X_2TTTTX_3X_4-3', wherein X_1, X_2, X_3 and X_4 are nucleotides and the T-rich nucleic acid comprises a phosphorothioate modification.

Liang et al teach a method of inducing an immune response (i.e., B cell proliferation) comprising administering a T-rich nucleic acid that is 100% T and is 20 nucleotides in length (see page 1122). Thus, the poly T nucleic acid of Liang comprises 5' TTTT 3', or 5'-X_1X_2TTTTX_3X_4-3', wherein X_1, X_2 are TT and X_3X_4 are TT and the poly T nucleic acid of Liang comprises at least 8 contiguous T nucleotide residues and at least 5 poly T motifs (i.e., TTTT). Further, the T-rich nucleic acid is free of CpG motifs whether methylated or unmethylated and is free of poly-C sequences. Because Liang et al teach a method of inducing an immune response and because innate immunity operates nonspecifically during the early phases of an immune response, it is the Examiner's position that Liang et al teach a method of inducing an innate immune response, wherein the active method step comprises administering a T-rich immunostimulatory nucleic acid. Thus, Liang et al anticipates the claims.

Conclusion

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571)

272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
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LARRY R. HELMS, PH.D
PRIMARY EXAMINER